Case Report

A case of syndromic congenital hypothyroidism with a 15.2 Mb interstitial deletion on 2q12.3q14.2 involving *PAX8*

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Highlights

- We report the identification and clinical characterization of a Japanese patient with CH who had a novel deletion involving *PAX8*.
- Patients with CH whose unifying diagnosis is not obvious could have a genomic deletion involving *PAX8*.

Abstract. Paired box 8 (*PAX8*) mutations are an established genetic cause of congenital hypothyroidism (CH). The majority of these mutations are found in the protein-coding exons of the gene. The proband, a 3-yr-old girl, had tetralogy of Fallot and polydactyly soon after birth. She was diagnosed with CH in the newborn screening for CH. She had a high serum TSH level (239 mU/L) and low free T4 level (0.7 ng/dL). Ultrasonography revealed thyroid hypoplasia. We performed array comparative genomic hybridization because the patient exhibited a variety of symptoms across multiple organ systems. The analysis revealed a novel heterozygous deletion that spanned a 15.2 Mb region in 2q12.3q14.3 (GRCh37; chr2:109,568,260–124,779,449). There were 71 protein-coding genes in this region, including two genes (*PAX8* and *GLI2*) associated with congenital endocrine disorders. The common clinical features of the two previously reported patients with a total *PAX8* deletion and our case were CH, short stature and intellectual disability, but the severity of hypothyroidism and other clinical features were variable. In conclusion, we describe a syndromic CH patient with a novel 2q12.3q14.3 deletion involving *PAX8*. Patients with CH, whose unifying diagnosis is not obvious, could have a genomic deletion involving *PAX8*.

Key words: chromosome deletion, *PAX8*, genetics, congenital hypothyroidism

Introduction

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder, affecting approximately 1 in 3,000–4,000 newborns (1). Thyroid hormone deficiency in infancy leads to irreversible intellectual disability but can be prevented by early diagnosis and treatment. Patients with CH can be classified into two major types, including patients with reduced thyroid tissue volume (thyroid dysplasia) and ones with goiter (thyroid dyshormonogenesis). The most common genetic form of thyroid dysgenesis is a genetic defect in the thyroid-specific transcription factor paired box 8 (PAX8). PAX8 is a member of the PAX gene family and is characterized by the presence of a DNA-binding paired domain at the N-terminus. In mice and humans, Pax8/PAX8 is expressed in the thyroid from the prenatal period to adulthood (2). Homozygous *Pax8*-knockout mice exhibit thyroid hypoplasia due to the abnormal proliferation and survival of thyroid precursor cells (3). To date, CH due to heterozygous loss-of-function *PAX8* mutations has been reported in 35 unrelated families with a total of 25 intragenic mutations (4–25) and two sporadic patients with total gene deletions (26, 27). Many patients with intragenic PAX8 mutations had a hypoplastic thyroid. Meanwhile, the clinical features of patients with total *PAX8* deletion are still poorly understood due to the limited number of cases. Here, we report the identification and clinical characterization of a Japanese patient with CH who had a novel deletion involving *PAX8*.

Case Report

The patient, a 3-yr-old girl, was born at 37 wk of gestation after an uneventful term pregnancy. Family history was non-contributory. Her birth weight was 2,712 g and length was 46.1 cm. Soon after the birth, she was noticed to have polydactyly of the left little finger but had no craniofacial anomalies. She had a heart murmur and was admitted to the Kurume University Hospital at the age of 7 d. She was diagnosed with tetralogy of Fallot, which was surgically corrected at the age of 3 yr. She also had a high blood-spot TSH level (> 80 mU/L; cutoff level, 10) at newborn screening for CH, and was consulted to pediatric endocrinologists at the age of 14 d. She had a high serum TSH level (239 mU/L; reference 1.7–9.1), a low serum free T_4 level (0.7 ng/dL; reference 0.9–2.3) and a high serum thyroglobulin (Tg) level (716 ng/mL; reference 3.8–56). She had hypotonia but no other CH-related manifestations, such as constipation, poor feeding and persistent jaundice, were noted. She was diagnosed with primary CH, and levothyroxine (L-T_4) replacement therapy was started at 13 µg/kg/d after the diagnosis. Ultrasonography was performed at the age of 1 mo with receiving L-T_4 therapy. Thyroid ultrasonography showed a normoechoic small thyroid gland (thyroid width, –4.0 SD) (28). Her kidneys were normal in size, structure and location. Brain magnetic resonance imaging (MRI) showed that the brain, including the hypothalamus and pituitary, was anatomically normal.

At the age of 11 mo, she had short stature (65.9 cm, –2.6 SD) and normal weight (7.8 kg, –0.4 SD) (**Fig. 1**). Her serum IGF-1 level was 33 ng/mL (age- and sex-specific reference interval, 15–154 ng/mL).

Her target height was 154 cm (–0.8 SD). She had moderate developmental delay: held her head up at the age of 5 mo, walked alone at the age of 1.9 yr, and used two-word sentences at the age of 3.3 yr. She had recurrent febrile and afebrile seizures since the age of 1 yr and was diagnosed with epilepsy based on abnormal electroencephalogram findings at the age of 3.3 yr. Levetiracetam was started to treat the epilepsy after diagnosis.

At the last clinical visit (age: 3.8 yr), she had a short stature (88.6 cm, –2.3 SD) with normal weight (13.3 kg, –0.4 SD) (**Fig. 1**). Her parents had normal stature (father: 163 cm, –1.4 SD; mother: 158 cm, –0.1 SD), and the target height of the patient was 154 cm (–0.8 SD). Considering the genetic potential, the short stature of the patient did not seem to be pathological. She was in biochemical euthyroidism with 3.0 µg/kg/d of L-T4. She did not have CH-related symptoms such as constipation, poor activity and poor weight gain.

Chromosome Analysis

G-banding analysis was performed using lymphocyte metaphase spreads (SRL, Inc., Tokyo, Japan). The analysis revealed an interstitial deletion involving long arm of chromosome 2, with a karyotype of 46,XX, del(2)(q12q14.2).

To completely evaluate the deleted region, we performed array comparative genomic hybridization (aCGH) analysis. Written informed consent was obtained from the parents of the patient, and the study protocol was approved by the ethics committee of the National Center for Child Health and Development (approval number: 553). Genomic DNA samples were obtained from peripheral leukocytes of the patient and subjected to oligonucleotide aCGH using a catalog microarray (SurePrint G3 Human CGH Microarray 4×180K; Agilent Technologies, Santa Clara, CA, USA). We confirmed the presence of a heterozygous deletion that spanned a 15.2 Mb region in 2q12.3q14.3 (GRCh37; chr2:109,568,260–124,779,449; **Fig. 2A**). Identical deletions have not been reported in the literature and are absent in the Database of Genomic Variants (http://dgv.tcag.ca/).

Discussion

In the present report, we describe a syndromic CH patient with 15.2 Mb interstitial deletion at 2q12.3q14.3. The deletion in our patient partially overlapped with that of two previous cases with a total *PAX8* deletion (**Fig. 2B**; previous case 1 (26) and previous case 2 (27)). The common deleted region of the two previous cases and ours spanned 10.8 Mb. Shared features of the three
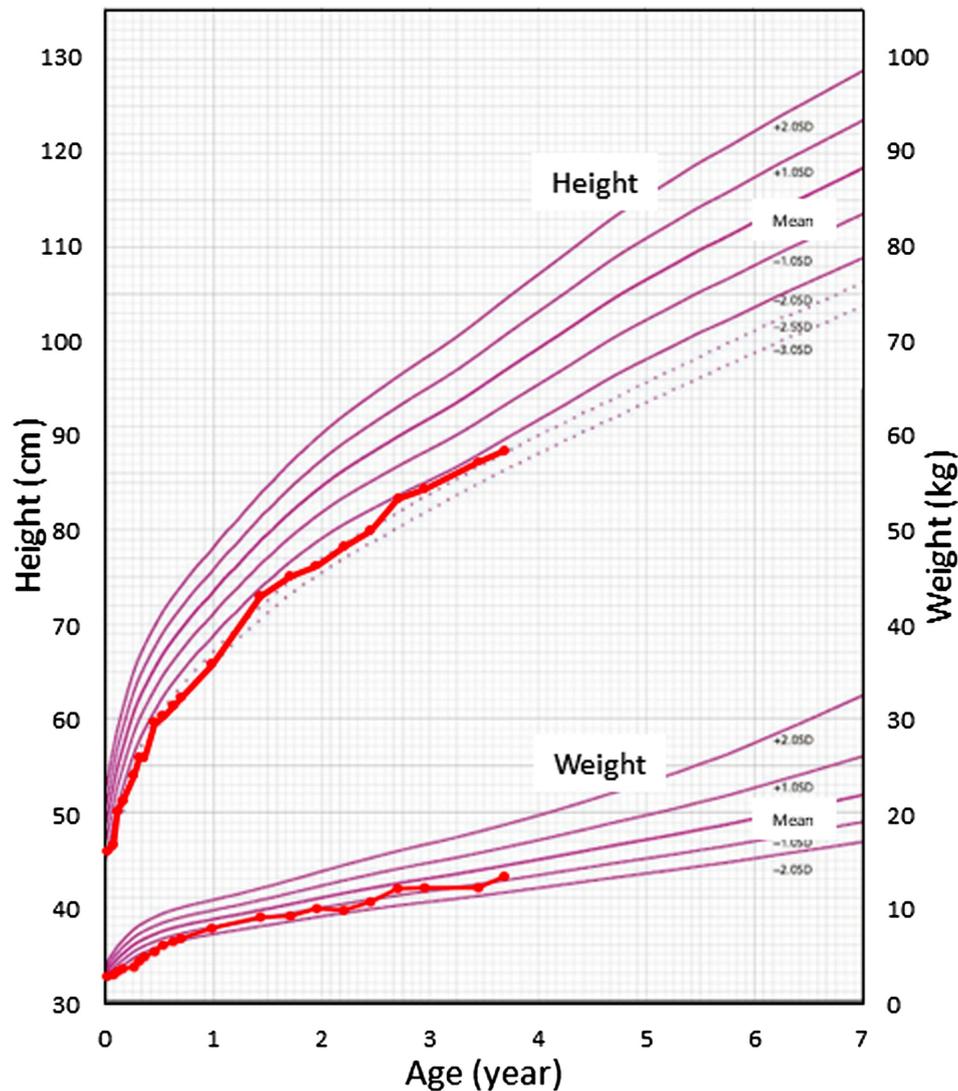
Fig. 1. Growth charts of the patient. The height and weight data of the patient are plotted on the Japanese standard growth charts for healthy Japanese girls in 2000. The upper chart shows height, and the lower chart shows weight. The curves depict +2.0 SD, +1.0 SD, Mean, –1.0 SD, –2.0 SD, –2.5 SD, and –3.0 SD of stature values.

cases were CH, short stature and intellectual disability (**Table 1**). Previous case 1 had moderate gross motor retardation with sitting alone at age 12 mo and walked alone at age 2.6 yr. Previous case 2 was reported to have mild intellectual disability, although detailed information on developmental milestone achievement was not available. In addition to CH, short stature, and intellectual disability, our patient had tetralogy of Fallot and polydactyly but did not have facial anomalies. Facial anomalies (e.g., deep-set eyes and bulbous nose) and clinodactyly were noted in Previous case 1. Previous case 2 had facial anomalies, including bilateral epicanthus and an atrial septal defect. The both of the two previous patients were female and had uterine agenesis and atresia of the upper portion of the vagina with normal fallopian tubes.

The deleted region in our patient included the 1.3-Mb common deleted region of 2q13 microdeletion syndrome (GRCh37; chr2:111,449,141–112,746,937) (29)

(**Fig. 2B**). The features of 2q13 microdeletion syndrome include intellectual disability, facial anomalies (e.g., hypertelorism and a flat nasal bridge), congenital heart defects, hypotonia and macrocephaly/microcephaly. The severity of intellectual disability varies from mild learning difficulty to moderate gross motor retardation. The correlation between the location/size of the deletion and clinical phenotypes in this syndrome remains to be elucidated.

The deletion in our case involves 71 protein-coding genes. Among the genes, autosomal dominant inheritance has been documented for *PAX8* and *GLI2*. We presume that these two genes could be responsible for the patient phenotypes. To the best of our knowledge, CH has never been reported in patients with the 2q13 microdeletion syndrome. This is probably because *PAX8* and putative distal enhancer(s) regulating its expression are not included in the commonly deleted region of the syndrome (**Fig. 2B**). The thyroid gland of our patient

A   Chromosome 2

B
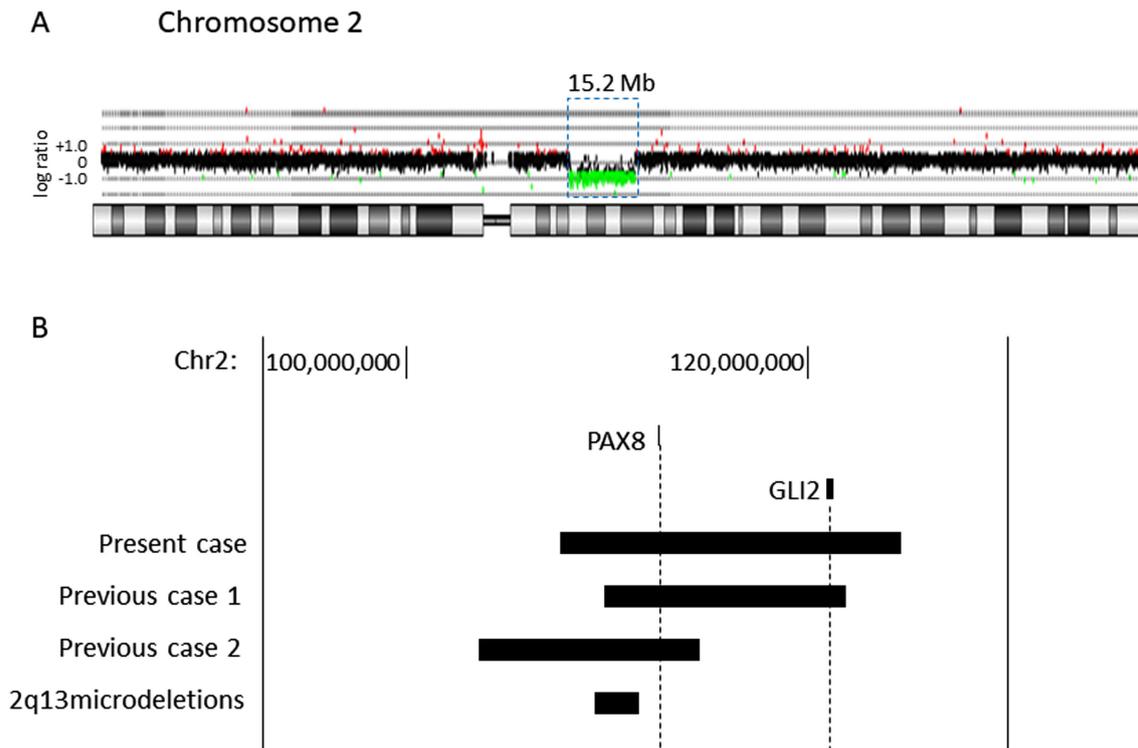
Fig. 2. A: Array-based comparative genomic hybridization showing 15.2 Mb heterozygous copy number variation (CNV) on chromosome 2. The green and red dots denote decreased (log ratio ≤ −0.8) and increased (log ratio ≥ + 0.4) copy numbers, respectively. B: Schematic diagram of the deleted region of patients with total *PAX8* deletion. The bottom part of the figure shows the most common deleted region of 2q13 microdeletion syndrome. The locations of two genes (*PAX8* and *GLI2*) are shown at the top of the figure.

Table 1. Clinical characteristics of total *PAX8* deletion and 2q13 microdeletion

	Present case	Previous case 1 (26)	Previous case 2 (27)	2q13 microdeletion syndrome (29)
Deleted region in chr 2 (GRCh37)	109,568,260–124,779,449	111,548,932–122,336,492	105,953,541–115,801,155	111,442,130– 113,007,823*
Sex	Female	Female	Female	Male, female
Short stature	Present Height SDS −2.3 (3 yr)	Present Height SDS −2.1 (12 yr)	Present Height data NA	Absent
Developmental delay	Moderate gross motor retardation	Moderate gross motor retardation	Mild intellectual disability	Variable (mild learning difficulty to moderate gross motor retardation)
Neurological findings	Hypotonia Epilepsy	Hypotonia	NA	Hypotonia
CH	Present Thyroid hypoplasia	Present Normal-sized thyroid	Present Thyroid hypoplasia	Absent
Other features	Tetralogy of Fallot Polydactyly	Aplasia of uterus and vagina Clinodactyly Facial anomalies	Aplasia of uterus and vagina Atrial septal defect Facial anomalies	Congenital heart defects Macrocephaly or microcephaly Facial anomalies

* Common deleted regions. CH, congenital hypothyroidism; NA, not available.

was hypoplastic. In the two previous cases with *PAX8* deletion, one had a normal-sized thyroid gland, while the other had thyroid hypoplasia (26, 27). Among the patients with an intragenic *PAX8* mutation, thyroid hypoplasia has been observed in approximately 75% of evaluated cases. Collectively, the thyroid phenotype of CH due to total *PAX8* deletions is not necessarily more severe than that due to intragenic *PAX8* mutations. Previous case 1 and 2 had uterine agenesis and atresia of the upper portion of the vagina with normal fallopian

tubes. Although there are no reports of patients with intragenic *PAX8* mutations exhibiting these symptoms, genetically engineered *Pax8*-knockout female mice have abnormalities in Müllerian duct-derived tissues, such as atresia of the uterus, vaginal opening, and impairment of the oviducts (30). Therefore, it is possible that the uterine and vaginal abnormalities in previous two cases may be due to the deletion of *PAX8*. The patient in this report should also be examined for uterine and vaginal abnormalities before puberty.

GLI2 encodes GLI Family Zinc Finger 2, which is a major effector protein of the sonic hedgehog pathway and plays a key role in development of the pituitary gland (31). Heterozygous loss-of-function *GLI2* mutations have been reported to cause pituitary anomalies (e.g., ectopic posterior pituitary and anterior pituitary hypoplasia with or without hypopituitarism), polydactyly, and craniofacial anomalies. Our patient had normal brain morphology with no craniofacial anomalies but had polydactyly and short stature with normal serum IGF-1 levels. *GLI2* was also deleted in Previous case 1, who had normal anterior pituitary gland function and no craniofacial anomalies but had clinodactyly and short stature. Genomic deletions encompassing *GLI2* have been reported in nine patients (26, 32–40), and their typical phenotypes were short stature, polydactyly and intellectual disability. Anterior pituitary gland functions were evaluated in five patients: one had panhypopituitarism, but the others had normal anterior pituitary gland function although they had short stature. MRI was performed in four patients, and all of them had anatomical abnormalities, including ectopic posterior pituitary, anterior pituitary hypoplasia and agenesis of corpus callosum. Holoprosencephaly was not observed in any of the four patients. Serum IGF-1 levels were measured in three patients, and two had normal levels. The phenotypes due to total *GLI2* deletion seem to be diverse. The short stature observed in carriers of total *GLI2* deletion is not necessarily to be accompanied by low serum IGF-1 levels. Our patient had short stature with normal serum IGF-1 levels and brain MRI findings. In our patient, appropriate follow-up of anterior pituitary function was required. Previous case 2 did not have *GLI2* deletion but had the Xp22.33 microdeletion involving *SHOX*. The short stature in Previous case 2 may be due to the *SHOX* haploinsufficiency.

In summary, we report on the third case of 2q12.3q14.3 deletion involving *PAX8* as a gene associated with CH. In CH patients with multiple congenital anomalies, whose unifying diagnosis is not obvious, chromosome structure mutations involving *PAX8* should be suspected.

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